DD3: A NEW PROSTATE SPECIFIC MARKER, OVEREXPRESSED IN PROSTATIC TUMORS.

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Prostate cancer is the most frequently diagnosed malignancy in the western male population. Likewise, in the Netherlands approximately 4500 males are diagnosed with prostate cancer, and more than 2200 die from this disease each year. When the tumor has locally or distantly spread, sadly enough no curative therapy can be offered. Therefore, detection of prostate carcinomas at an early stage, when curative intervention is possible, is important. A better understanding of the molecular changes associated with the onset and progression of prostate cancer might provide a rational basis to develop new diagnostic tools and potentially new therapeutical strategies.

Differential display analysis was used to identify genes that are differentially expressed between benign and malignant tissues of the prostate. We thus identified DD3, which on Northern blot detects two transcripts that are specifically expressed in (38/41) human prostatic tumors whereas no expression of these transcripts is found in normal prostate or benign prostatic hyperplasia (BPH) tissue from the same patients. Nucleotide sequence analysis of DD3 did not reveal an open reading frame nor did we find homology with any known gene. Isolation of additional DD3-related cDNA and genomic clones allowed a further characterization of the transcription unit of DD3 and revealed that alternative splicing occurs, which may be one of the mechanisms giving rise to the differently sized transcripts. Using the DD3-related genomic clones as probes, we were able to map DD3 to chromosome 9q21-22, a region which (by comparative genomic hybridization) was shown to be amplified in a number of prostatic tumors, suggesting that overexpression of the gene may be a result of gene amplification. Upon developing DD3-specific primers for RT-PCR analysis, we were able to show that DD3 expression is very prostate specific since no DD3 transcripts could be detected in normal human artery, breast, bladder, colon, duodenum, heart, kidney, liver, lung, pancreas, seminal vesicles, skin, spleen or testis. Also in 6 of 7 human prostate cancer cell lines studied no DD3-related PCR product could be amplified. Other genes whose expression has been reported to be restricted to the prostate include PAP (prostate acid phosphatase), PSA (prostate-specific antigen), PSM (prostate-specific membrane antigen) and prostate-specific transglutaminase. PSA is currently used as a serum marker for prostate cancer, however, PSA is not always able to distinguigh prostate cancer from benign prostatic hyperplasia (BPH). We are currently investigating whether DD3 is a more specific marker for prostate cancer than are PSA and PSM.

Further molecular characterization of DD3 will be important to develop useful diagnostic tools for early detection of prostate cancer and to investigate its potential as target for gene- and/or immunotherapy.

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